REMARKS/ARGUMENTS

Claims 531-542, 544-548 and 550-576 are pending. Claims 531-532, 534, 536-538, 541, 544, 547, 558 and 569 have been amended herein. Support for the amendments to Claim 547 may be found at page 17, lines 4-15, of the present application. Claims 543 and 549 have been cancelled without intending to abandon or to dedicate to the public any patentable subject matter. As set forth more fully below, reconsideration and withdrawal of the Examiner's rejections of the claims are respectfully requested.

Objections to the Specification

The Examiner has objected to the specification as containing an embedded hyperlink at page 41, line 10. Applicants have amended the specification to delete this hyperlink.

Rejections Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected Claims 531-576 under 35 U.S.C. § 112, first paragraph, as lacking enablement in the specification for the full scope of the claims. In determining this issue of enablement, the Examiner analyzes the eight factors listed in *In re Wands*, 8 USPQ2d (Fed. Cir. 1988) and concludes that undue experimentation is required by one of skill in the art to practice the invention "because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching, and guidance presented." Further, the Examiner states that absent "factual data to the contrary, the amount and level of experimentation needed is undue."

Applicants are submitting herewith the Declaration of Dr. David Bar-Or ("Bar-Or Declaration"). The Bar-Or Declaration describes the testing of a total of thirty-two peptides coming within the scope of the rejected claims. The peptides of the present invention operate by a common mechanism of metal binding, and all of the thirty-two peptides possess at least one metal-binding site. The peptides vary by size of the peptide, sequence of the peptide (including different sizes and types of amino acids), hydrophobicity, hydrophilicity and other features. The

peptides were tested in a variety of assays to demonstrate their ability to bind copper and inhibit angiogenesis.

First, the peptides were tested for their ability to inhibit the production of hydroxyl radicals caused by copper ions (see, *e.g.*, page 64, lines 13-28, of the present application for a description of the reactions). The results are presented in Examples 7 and 10 in the present application and in the Bar-Or Declaration, paragraph 3 and Exhibit A. As can be seen from the results, a wide variety of peptides coming within the scope of the rejected claims are effective in inhibiting the production of hydroxyl radicals, showing that the peptides have the ability to inhibit a copper-mediated reaction and confirming their ability to bind copper ions. See also, paragraph 6 of the Bar-Or Declaration and Exhibit D attached thereto, which describe the determination of the copper-binding stability constants of eleven of the peptides. These stability constants provide further evidence that the peptides of the invention bind copper strongly.

Next, the peptides were tested for their ability to inhibit the release of interleukin-8 (IL-8) from human umbilical vein endothelial cells (HUVECs). The results are presented in the Bar-Or Declaration, paragraph 4 and Exhibit B. As can be seen from the results, a wide variety of peptides coming within the scope of the claims are effective in inhibiting the release of IL-8 from HUVECs. IL-8 is a potent promoter of angiogenesis. It has been reported that IL-8 induces the migration of endothelial cells, induces the proliferation of endothelial cells and induces neovascularization, and that inhibition of IL-8 inhibits angiogenesis. See, *e.g.,* Simonini et al., *Circulation*, **101(13)**:1519-1526 (2000); Keane et al., *J. Immunol.*, **159(3)**:1437-1443 (1997); Arenberg et al., *J. Clin. Invest.*, **97(12)**:2792-2802 (1996); Smith et al., *J. Exp. Med.,* **179(5)**:1409-1415 (1994); Streiter et al., *Am. J. Pathol.*, **141(6)**:1279-1284 (1992) (copies of abstracts being submitted herewith). Thus, the results of the experiments described paragraph 4 and Exhibit B of the Bar-Or Declaration provide strong evidence that the peptides of the invention have the ability to inhibit angiogenesis.

There are three distinct stages in angiogenesis: (i) endothelial cell proliferation, representing the initial build up of cell mass after initiation of angiogenesis; (ii) endothelial cell

migration toward the angiogenic site following a chemotactic gradient; and (iii) differentiation and assembly of endothelial cells to form tube like structures in a three-dimensional space. The thirty-two peptides were tested for their ability to inhibit the proliferation of HUVECs. The results are presented in the Bar-Or Declaration, paragraph 5 and Exhibit C. It can be seen from the results that most of the peptides were effective in inhibiting the proliferation of HUVECs. These results provide additional evidence that the peptides of the invention have the ability to inhibit angiogenesis.

Finally, nine of the peptides were tested in the chicken chorioallantoic membrane (CAM) assay which measures angiogenesis in fertilized eggs. The results are presented in the Bar-Or Declaration, paragraph 7 and Exhibit D. See also Example 12 in the present application. As can be seen from the results, all nine of the peptides inhibited angiogenesis in this *in vivo* assay. These results are all the more remarkable since it has now been determined that the peptides tested in the experiments described in the Bar-Or Declaration were inadvertently supplied at a concentration substantially less than needed to bind the quantity of copper present in the eggs. See Bar-Or Declaration, paragraph 7. Thus, the results demonstrate that the peptides of the invention inhibit angiogenesis *in vivo*, and it is expected that even better results should be obtained with higher concentrations of the peptides sufficient to bind the copper present in the eggs.

The foregoing demonstrates that a wide variety of peptides coming within the scope of the claims are effective in inhibiting angiogenesis, including *in vitro* assays for inhibition of pro-angiogenic factors and processes and an *in vivo* assay. As described in the application and shown by the data in the Bar-Or application, all of the peptides covered by the claims, including the tested peptides, operate by a common mechanism of metal binding. Therefore, in view of the test data, it can be expected that all of the peptides covered by the claims will be effective in inhibiting angiogenesis. Applicants submit that the data presented in the Bar-Or Declaration confirm and establish that the guidance presented in the specification is sufficient to enable one of skill in the art to make and use the invention as currently claimed without undue experimentation.

Specifically, to address the eight *Wands* factors analyzed by the Examiner in light of the amendments to the claims and the Bar-Or Declaration:

1) The nature of the invention: Applicants submit that the Examiner has correctly stated the nature of the invention as recited in Claim 531, although Applicants note that the claimed invention has been narrowed by amendments to Claim 531 made in this Amendment and Response.

2) The breadth of the claims: As noted above, Applicants have narrowed the breadth of the claims by restricting the claimed peptides to those peptides wherein P_2 is $(Xaa_4)_n$ and n is 0-10. This amendment substantially decreases the peptides encompassed by the formula for the metal-binding peptide.

3) The predictability or unpredictability of the art: In the analysis of this factor, the Examiner cites Lane (Lane et al., *J. Cell Biol.* **125(4)**:929-43 (1994)) as teaching that SPARC and a peptide sequence (KGHK) within SPARC are capable of binding copper and stimulating angiogenesis. With respect to this factor, the Examiner concludes that "there is no way to predict whether all of the metal-binding peptides encompassed by the formula of claim 531 will treat an angiogenic disease or condition by inhibiting angiogenesis."

Initially, Applicants note that the results of Lane show that the angiogenic activity of SPARC was marginal but that stimulation of capillary growth was restricted to the KGHK fragment of SPARC or longer peptides that contained the KGHK sequence internal to the peptide (see the last paragraph of the introductory section of Lane as well as the results described at the bottom of page 932 through the second column of page 934). Thus, the angiogenic activity reported by Lane is specific to the sequence KGHK and Applicants have amended the pending claims to remove the KGHK peptide of Lane by deleting glycine from the definition of Xaa_2.

Applicants submit that in light of these amendments and the experimental results reported in the Bar-Or Declaration that demonstrate the inhibition of angiogenesis by a wide range of peptides covered by the instant claims, the anti-angiogenic activity of the claimed peptides can be reliably predicted.

4) & 5) The amount of direction or guidance presented: The presence or absence of working examples: The Examiner states that the specification provides no guidance in selecting peptides having the claimed activity in treating angiogenic diseases. This analysis by the Examiner is based on the number of working examples provided in the disclosure. Specifically, the Examiner notes that only one example (Asp-Ala-His-Lys) is provided in the specification. As described in section 2164.02 of the MPEP, the enablement requirement does not turn on the whether an example is disclosed and, when one or more working examples are provided, applicant need not describe all actual embodiments. In the instant application, the specification provides one working example and Applicants submit herewith the Bar-Or Declaration that provides an additional 70+ working examples demonstrating the efficacy of the claimed family of metal binding peptides. Thus, Applicants have now provided in excess of 70 working examples and therefore submit that there is certainly sufficient working examples of record to support a finding of enablement of the currently pending claims.

6) The quantity of experimentation necessary: The Examiner states that there is a large quantity of experimentation necessary to determine which peptides are capable of inhibiting angiogenesis. As noted above, Applicants submit herewith the Bar-Or Declaration that demonstrates the anti-angiogenic activity of at least 32 claimed peptides which comprise a wide variety of different types of peptides, thereby providing a substantial portion of the testing of every claimed peptide and further indicating that the results of this significant subsection of the claimed peptides can be extrapolated to the entire family of claimed metal binding peptides.

7) The state of the prior art: In the analysis of this factor, the Examiner cites Brewer (*Clin. Cancer. Res.* **6**:1-1 (2000)) as disclosing that antiangiogenic treatments show efficacy in animal tumor models and that copper is required for angiogenesis. But the Examiner notes that the authors also hypothesize that very rapidly progressing large tumors may be poor candidates for antiangiogenesis therapy as a single modality because of the ability of these tumors to sequester copper. Thus, the Brewer authors suggest that chelating agents may have unpredictable results for large (*i.e.* advanced), rapidly growing/metastasizing (*i.e.* very aggressive) tumors

treated with only one agent. Applicants submit that this is consistent with the prior art for all single drug cancer therapies and that no anti-cancer compound currently in clinical use is routinely and predictability effective in the treatment of advanced, aggressive tumors (*i.e.* end stage tumor therapy) when used as a single drug therapy. Thus, the statements in Brewer describing the efficacy of antiangiogenic treatments as effective in tumor models but theoretically ineffective as a single entity treatment of advanced, aggressive tumors suggests an efficacy similar to most modern antineoplastic compounds. This supports the enablement of the use of the currently claimed peptide anti-angiogenic compounds for the treatment of most neoplastic diseases as a single agent or combined with other treatments as part of a therapeutic reigmen.

8) The level of skill in the art: Applicants agree with the Examiner's evaluation that level of skill in the art is high.

Thus, in re-considering these eight factors in view of the claim amendments herein and the experimental evidence provided in the Bar-Or Declaration, Applicants submit that there is adequate enablement of record for Claims 531-576, as amended, and request the Examiner's rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

Claim Rejections Under 35 U.S.C. § 102

The Examiner has rejected Claims 531, 532, 534-536, 541, 543-545 under 35 U.S.C. § 102(b) being anticipated by Lane (Lane et al., J. *Cell Biol.* **125(4)**:929-943 (1994)). The Examiner notes that Lane teaches the stimulation of angiogenesis in response to the administration of the peptide KGHK and contends that Lane, therefore, discloses a method of treating an angiogenic disease or condition comprising administering the copper-binding peptide KGHK. As noted above, the angiogenic activity reported by Lane is specific to the sequence KGHK, and Applicants have amended the pending claims to delete glycine from the definition of Xaa_2, so that the claims no longer cover the KGHK peptide of Lane.

Based upon the foregoing, Applicants believe that all pending claims are in condition for

allowance and such disposition is respectfully requested. In the event that a telephone conversation would further prosecution and/or expedite allowance, the Examiner is invited to contact the undersigned.

Respectfully submitted,

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